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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,550	12/19/2000	Julia Y. Ljubimova	18810-80364	6437

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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/741,550	LJUBIMOVA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on March 24, 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-10,13-18,21-29,32-36,44,45,48-68 and 75-78 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10,13-18,21-29,32-36,44,45,48-68 and 75-78 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. This action is in response to the papers filed March 24, 2003. Currently, claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are pending.
2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and the arguments.

### ***Election/Restrictions***

4. Applicant's election without traverse of Group II (Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78) in Paper No. 7 is acknowledged.
5. Upon reconsideration, the restriction requirement between the mRNA and the protein of laminin alpha4 has been withdrawn. Given the data in Figure 5 and the information in Table 7, the mRNA and the protein appear to be correlative. Furthermore, the specification states that "these results were in complete accordance with the gene array analysis and the RT-PCR" (page 50, lines 25-26). Therefore, a method of detecting a mRNA and protein would not be patentably distinct. Therefore, the restriction has been withdrawn.

***Specification***

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

For example, page 20, line 2, a link is included.

***Claim Rejections - 35 USC § 112- Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a glioma in a human subject by detecting quantitatively or semi-quantitatively a level of expression of laminin alpha4-specific mRNA or protein, does not reasonably provide enablement for detecting any malignant tumor, including breast and prostate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to methods for detecting any malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA to

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normal controls, wherein overexpression of laminin alpha4-specific mRNA indicates the presence of a malignant tumor.

The art, namely Ringelmann et al. (Experimental Cell Research, Vol. 246, pages 165-182, 1999) teaches strong interstitial expression of laminin alpha4 mRNA in myogenic tissues of embryonic but not mature mice, implicating a role for this laminin alpha chain in myogenesis (page 166, col. 2). Additionally, Previtali et al. (Glia, Vol. 26, pages 55-63, 1999) teaches the abnormal expression of a laminin receptor, alpha6beta4 integrin in human astrocytomas (abstract). Tysnes et al. (Int. J. Devl. Neuroscience, Vol. 17, No. 5-6, pages 531-539, 1999) teaches "compared to normal astrocytes, neoplastic astrocytes in situ have shown increased expression of the laminin receptor alpha3 and beta1 integrin subunits" (page 538).

With respect to Claims 28-29, 32-36, 44-45, 48-59 directed to a method of predicting the recurrence of a malignant tumor in a human from whom a tumor has been resected, the fails to provide any analysis directed to recurrence of a malignant tumor. The specification does not provide any predictable correlation between recurrence of a malignant tumor and expression analysis. While the skilled artisan could provide an analysis of region adjacent to the site of the tumor and analyze their expression of laminin alpha4, the results of such experiment would be unpredictable.

With respect to Claims 60-66 directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The specification has provided no guidance as to what the "relatively high invasiveness of the tumor" encompasses. The specification seems to

illustrate a few examples where laminin alpha4 is overexpressed in astrocytoma grade II. The specification teaches that astrocytoma grade II is a lower grade malignant tumor (page 11, lines 15-16). Therefore, it is unclear how the overexpression of laminin is indicative of relatively high invasiveness of the tumor. The claims does not appear to make any distinction between low grade and higher grade tumors. Therefore, it is unclear how the tumors are classified. While the skilled artisan could provide further undue experimentation to determine a value for expression in the various types of tumors and obtain thresholds for classifying the tumors, the instant specification does not provide any predictive correlation between thresholds and classifications of tumors into grades, as required by the claims.

Moreover, the specification provides no guidance to the skilled artisan how to use the invention with respect to any type of malignant tumor. The specification does not teach expression levels in all malignant tumors, including breast, prostate, lung, colon, etc. While one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, do not provide support for the use of laminin alpha4 expression as an indicator of malignant tumor. Thus it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide

evidence of a correlation or association between laminin alpha4 expression and malignant tumors, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

### **Response to Arguments and Declaration**

The response traverses the rejection.

First, it is noted that the enablement rejection has been deemed to be a scope of enablement rejection upon review of applicant's remarks. Upon review of the remarks and the specification, the level of expression in laminin alpha4 mRNA and protein appear to be correlative with gliomas (see Figure 5 and Table 7). Each of these showings demonstrate that there is differential expression between gliomas and normal tissues. Therefore, claims drawn to gliomas would be enabled.

The response asserts that the relation between vascular tissue and alpha4 laminin suggest a mode by which this structural gene can be related to malignancy. The response specifically directs attention to the Declaration from Dr. Ljubimova. The response asserts that the instant invention is directly applicable to breast malignancy and prostate malignancy. This argument has been reviewed but is not convincing because upon analysis of the declaration, the declaration does not appear to support the conclusions.

It is noted that the response points out that "Table 7 deals with detection of actual protein (as opposed to nucleic acids) which detection is covered by the non-elected claims and, hence, Table 7 does not directly apply to the claims in prosecution." (Page

22 of Response filed March 24, 2003). The Declaration filed is solely directed to Western Blots which detect protein. Since the restriction requirement has been withdrawn, the Declaration will be considered to determine whether the protein levels are correlative in additional malignancies.

The Declaration states that "like brain malignancies, malignant tumors of the breast overexpress alpha4 laminin." (page 2 of Declaration filed March 24, 2003). The specification makes clear that the laminin alpha4 subunit is particular to laminin-8, laminin-9 and laminin-14 (page 5, lines 17-19). The data in the Declaration illustrates that Laminin-8 is not expressed in normal tissue, but appears expressed in invasive carcinoma, metastases of invasive carcinoma and non-invasive carcinomas. However, Laminin-9 does not appear to be correlative of the same expression pattern. Laminin-9 is expressed in normal breast tissue (40%). This appears to indicate that the alpha4 subunit may not be responsible for the expression in breast tissues. The response argues on page 23 of the Response that "Laminin 8 requires an overexpression of both alpha4 and beta1 subunits." Therefore, the expression of Laminin 8 in breast, but not in normal may be due to the beta1 subunits since Laminin 9 does not have the same correlation. Furthermore, the data provided in the table is not quantitative or semi-quantitative in nature. Unlike Table 7 in the specification, the Declaration has not provided any intensities.

While the Declaration asserts, "My studies show that prostate malignancies, like those of the brain and the breast also overexpress alpha4 laminin." (Page 3 of the Declaration filed March 24, 2003). This statement is confusing because while the brain



malignancies appear to be associated with alpha4 laminin, the data provided in the Declaration do not appear to support the overexpression of alpha4 laminin in breast malignancies. Therefore, without further information and data, the examiner is unable to evaluate the data regarding prostate malignancies.

With regard to the data presented on Page 4 of the Declaration, the western blot appears to show a lack of laminin alpha4 chain expression in normal breast tissue and its strong expression in breast cancer metastases. The Figure illustrates that the metastasis are "brain metastasis of breast cancer." Therefore, the results of the of the Figure appear to support a brain metastasis of breast cancer, but does not support breast cancer malignancies. As stated previously, while one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

With respect to Claims 28-29, 32-36, 44-45, 48-59 the response argues that the data shows a high degree of correlation between the analysis and the clinical outcome. This argument has been thoroughly reviewed, but is not found persuasive because the claims are directed to a method of predicting the recurrence of a malignant tumor in a human from whom a tumor has been resected. There is no data in the specification which analyzes a tissue in which the tumor has been resected. There is no indication that tumors will recur once they were cut out if there is overexpression of the alpha4 laminin. With out performing additional experimentation on individuals yet to develop

recurrent tumors, it is unpredictable whether the overexpression in the adjacent tumors is indicative of recurrence.

With respect to Claims 60-66, the response argues that directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. First, the claims require "at least one specific to a growth factor-related gene or to a structural gene other than a laminin gene." The response appears to asserts that the claim is directed to beta1 subunits because the response state "this being the other overexpressed structural gene." Therefore, the response does not appear to be arguing what is claimed. Moreover, the claim is drawn to a method of establishing a grade by comparing expression profiles by comparing expression profiles. The response appears to be directed to a method of arraying samples in an order to determine the claimed grade. The method argued in the response appears to be a method of determining how to establish the grade of tumors rather than establishing the grade of a tissue from a human. The method as amended does not provide any indication of how to put a grade on a tumor. The method merely describes a generic method for assessing grades such that the higher the expression the higher the grade. Claims 60-66 do not appear to reflect the invention being argued by the response. The specification has not provided any guidance to the skilled artisan how to establish the grade of a malignant tumor. There are not specifics in the description what various grades of tumors encompass. Therefore, the skilled artisan would not be able to establish the specific grade of a tumor with out further experimentation.

Thus for the reasons above and those already of record, the rejection is maintained.

***Claim Rejections - 35 USC § 112- Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 60-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

C) Claims 60-66 are indefinite because the preamble is directed to a method of establishing the grade of a malignant tumor, however the final process is directed to indicating the presence and relatively high invasiveness/agressiveness of the tumor. The claims does not provide any means for establishing the grade of a malignant tumor. Grading generally requires placing the items into several different categories. The claims provide no guidance to how to classify the grade of a malignant tumor. Therefore, it is unclear whether the claim is directed to establishing the grade of a malignant tumor or whether the claim is directed to predicting "invasiveness". The method appears to be a method which establishes whether the tumor is more aggressive or invasive than normal tissue, which does not appear to be the invention argued by the response. The metes and bounds of the claimed invention are unclear.

***Conclusion***

9. No claims allowable.

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10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

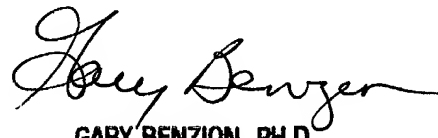
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Jeanine Goldberg  
June 5, 2003

  
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